REMARKS

Claims 89-110 were pending prior to this Response. By the present communication, claim 99-100 and 106-107 have been canceled without prejudice or disclaimer; claims 93 and 105 have been amended; and claims 111-130 have been added. The amendments and new claims do not raise any issues of new matter being fully supported by the specification and claims as filed. Support for added claims 111-130 may be found, among others, at paragraphs [0024], [0031], [0039], [0050], and [0095]. Thus upon entry of the present amendment, claims 93 and 101-105 and 108-130 will be pending in this application.

Claim Objections

The Examiner has objected to claims 105-110 for the following alleged informality: GM-CSF should first be identified by it's full name followed by the abbreviation in parenthetical. Applicants have canceled claims 106-107 rendering the objection moot as to these claims. Without acquiescing to the Examiner's reasoning, Applicants have amended the claims as the Examiner has suggested. In light of the amendments made, Applicants respectfully assert that the objection is moot, and request withdrawal of the objection.

Rejections under 35 U.S.C. §112, First Paragraph

Applicants respectfully traverse the rejection of claims 99-100 and 106-107 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants have canceled claims 99-100 and 106-107 rendering the rejection moot. However, Applicants traverse the rejection as it may apply to new claims 111-130.

Applicants traverse the allegation in the Office Action that peptide SEQ ID NO:7 has allegedly "not been shown to have any of anti-inflammatory or anti septic activity [OR even antimicrobial activity/immune system stimulation (the claimed invention), alone and absent the antibiotic or granulocyte-macrophage colony stimulating factor (GM-CSF)...."

The Action alleges that SEQ ID NO:7 has not been shown to have anti-inflammatory activity. Applicants respectfully disagree and submit that the specification clearly teaches the anti-inflammatory activity of SEQ ID NO:7, and related peptides. Support for anti-inflammatory activity can be found, for example, in the specification at Table 4 (paragraph [0095]). Table 4 discloses the reduction of *E. coli* lipopolysaccharide (LPS) induced TNF-α production in mouse macrophage cells by cationic peptides. Macrophage cells treated with SEQ ID NO:7 were shown to have approximately 50.5% decreased tumor necrosis factor-α (TNF-α) production as compared to untreated cells. The role of TNF-α as a pro-inflammatory cytokine and its link to initiating inflammation, is described in the specification in paragraph [0007], as well as being known to one skilled in the immunological arts. Paragraph [0007] discloses the following:

> The presence of microbial components induce the release of pro-inflammatory cytokines of which tumor necrosis factor-α (TNF-α) is of extreme importance. TNF-α and other pro-inflammatory cytokines can then cause the release of other pro-inflammatory mediators and lead to an inflammatory cascade.

Clearly, the demonstrated ability of SEQ ID NO:7 to drastically reduce levels of TNF-α in light of the relevant teachings of the role of TNF-α in the specification enables one skilled in the art to recognize the anti-inflammatory activity of the peptide.

The Action further alleges that SEQ ID NO:7 has not been shown to have anti-sepsis activity. Applicants respectfully disagree and submit that the specification clearly teaches the anti-sepsis activity of SEQ ID NO:7, and related peptides. Applicants respectfully direct the Examiner to Table 11, which demonstrates protection against lethal endotoxaemia in galatosamine-sensitized CD-1 mice using cationic peptides. Table 11 shows a 40% survival rate of CD-1 mice treated with SEQ ID NO:6 as compared with untreated mice in which endotoxic shock was induced by intraperitoneal injection of *E.coli* LPS. Additionally, paragraph [0007] of the specification, teaches that "gram-negative sepsis is usually caused by the release of bacterial outer membrane component, lipopolysaccharide...." The demonstrated ability of SEQ ID NO:6

to increase the survival rate from 0% to 40% in response to bacterially induced sepsis, clearly shows anti-sepsis activity.

Applicants respectfully submit that one skilled in the art would expect peptides SEQ ID NO:6 and SEQ ID NO:7 to act similarly; especially in view of their similar efficacies as disclosed in Table 4 and similar general formula as described in [0057] of the specification. Table 4 indicates that the inhibition rate of TNF-α by SEQ ID NO:6 and SEQ ID NO:7 is very similar, approximately 59.8% and 50.6%, respectively. Applicants respectfully submit that in view of the teachings of the specification, the demonstrated anti-sepsis activity of SEQ ID NO:6, and the demonstrated similar activities of SEQ ID NO:6 and SEQ ID NO:7 to inhibit production of TNF-α, the anti-sepsis activity of SEQ ID NO:7 is sufficiently enabled and described in such a way as to enable one skilled in the art to make or use the invention.

The Action further alleges that SEQ ID NO:7 has not been shown to have immune system stimulatory activity (efficacy against infection). Applicants respectfully disagree and submit that the specification clearly teaches immune system stimulatory activity of SEQ ID NO:7, and related peptides. Applicants respectfully direct the Examiner to Tables 50 and 51 of the specification disclosing the effect of cationic peptides on *Salmonella* and *S. aureus* infection, respectively. Table 50 shows bacterial counts in the spleens of mice infected with *Salmonella*. *Salmonella* infected mice treated with SEQ ID NO:7 had bacterial counts of approximately 5.4 x 10^3 CFU/ml while mice not treated with SEQ ID NO:7 had bacterial counts significantly higher at approximately 1.88 x 10^4 CFU/ml. Table 51 shows bacterial counts in blood of mice infected with *S. aureus*. *S. aureus* infected mice treated with SEQ ID NO:7 had bacterial blood counts of approximately 3.8 x 10^3 CFU/ml while those not treated with SEQ ID NO:7 had bacterial counts significantly higher (almost double) at approximately 7.6 x 10^3 CFU/ml.

Additionally, evidence of the ability of SEQ ID NO:7 to act as an immune system stimulant is disclosed in Example 12 and corresponding Figure 1 of the specification, which

demonstrate the synergistic combination of SEQ ID NO:7 and the antibiotic cefepime to inhibit systemic *S. aureus* infection. The Action remarks that the only conclusion to be drawn from Example 12 is that SEQ ID NO:7 works synergistically with the antibiotic to improve *S. aureus* infection but is allegedly not conclusive as to whether SEQ ID NO:7 can stimulate innate immunity. Applicants respectfully direct the Examiner's attention to the group of mice administered SEQ ID NO:7 alone and not in combination with antibiotic as evidenced in Figure 1 and Example 12. Such mice had bacterial blood counts of less than 10,000 CFU/ml while mice not treated with either peptide or antibiotic had bacterial blood counts of over 15,000 CFU/ml. Applicants respectfully submit that the specification clearly demonstrates SEQ ID NO:7 as having immune system stimulatory activity (efficacy against infection), as is evidenced in the aforementioned examples.

As additional support to show the anti-inflammatory activity, anti-sepsis activity and immune system stimulatory activity (efficacy against infection), of SEQ ID NO:7, Applicants submit herewith the declaration of Dr. Oreola Donini, Senior Director of Preclinical Research and Development at Inimex Pharmaceuticals Inc. Included in the declaration are the following exhibits: 1) a scientific publication (Scott et al., Nature Biotechnology, 25: 265-472 (April 2007)) (Exhibit A); 2) a report written by Dr. Donini presenting experimental data of infection model studies using peptides and methods of the claimed invention (Exhibit B); and 3) the curriculum vitae of Dr. Donini (Exhibit C). Specifically, the report (Exhibit B) describes various infection models using peptides of the claimed invention (SEQ ID NO:6 and SEQ ID NO:7) demonstrating anti-inflammatory activity, anti-sepsis activity, and immune system stimulatory activity (efficacy against infection).

As indicated by Dr. Donini, Exhibit A discloses cationic peptides that exhibit anti-infective properties, including SEQ ID NO:7. The publication also shows the peptides' ability to selectively modulate the innate immune response along with their mechanism of action. SEQ ID NO:7 is demonstrated to be protective in a broad range of *in vivo* infection models by local and

systemic administration, and is shown not to be directly antimicrobial but to act instead on the host innate immune system. The mechanism of action of SEQ ID NO:7, and related peptides, is presented showing that SEQ ID NO:7 activates several signaling pathways, stimulates transcription factors and sustains or enhances the levels of infection-clearing chemokines, while suppressing levels of pathogen-associated pro-inflammatory cytokines such as TNF-α without being toxic.

With regard to anti-inflammatory activity, Dr. Donini presents evidence of *in vivo* infection models and acute inflammation models demonstrating that SEQ ID NO:7 is capable of decreasing inflammation. Data in Figures 6-9 of Exhibit B of the declaration clearly indicate that in addition to aiding in the resolution of infection, SEQ ID NO:7 and related peptides are simultaneously able to modulate inflammation.

With regard to anti-sepsis activity, Dr. Donini presents evidence that implicates SEQ ID NO:7 as having anti-sepsis activity as an extension of its anti-inflammatory activity (see Figures 10 and 11 of Exhibit B of the declaration). This is demonstrated by the up-regulation of CCL5 by SEQ ID NO:7 (Figure 10 of Exhibit B of the declaration), a positive prognosticator of sepsis outcome in a clinical setting, and by the activity of the related peptide, SEQ ID NO:6 to prolong survival in a sepsis model (Figure 11 of Exhibit B of the declaration). As previously discussed, both SEQ ID NO:6 and SEQ ID NO:7 would be expected to act similarly to reduce sepsis in view of their efficacy in reduction of *E.coli* LPS induced TNF-α production as shown in Table 4 of the specification. Similarly, both peptides would have similar anti-inflammatory properties and similar abilities to confer innate immunity to a host.

With regard to the immune system stimulatory activity of SEQ ID NO:7, Dr. Donini presents evidence demonstrating the efficacy of SEQ ID NO:7 in a number of infection models, with multiple pathogens, routes of administration and dosing regimes (Figure 1-5 of Exhibit B of the declaration). Because SEQ ID NO:7 and the other cationic peptides presented in the

specification do not function by direct bacterial killing, as discussed in Scott et al. (Exhibit A of the declaration), the results of the infection models serve as an important demonstration of the ability of the peptide to induce a "protective" host response against a very acute and rapid infection.

Applicants respectfully submit that the specification is fully enabled for anti-inflammatory activity, anti-sepsis activity and immune system stimulatory activity in light of the present specification, the additional experimental data provided in the declaration by Dr. Donini and the knowledge in the immunological arts at the time of filing. As such, one skilled in the art would have been capable of performing the additional routine infection models as presented in the declaration, as such models are well known in the art as well as being taught in the specification. Additionally, one skilled in the art would have understood that the peptides described in the specification, in light of their demonstrated capacity to reduce pathogen mediated TNF-α production and to regulate various immune response pathways, would have been capable of exhibiting anti-inflammatory activity, anti-sepsis activity, and conferring innate immunity. Given the links between infection and the inflammatory response and sepsis, one of skill in the art would have understood that the inventors were in possession of the complete invention without further undue experimentation.

Rejections under 35 U.S.C. §112, Second Paragraph

Applicants respectfully traverse the rejection of claims 93 and 99-104 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action alleges that it is unclear what the invention covered by the scope of claim 93 is, as opposed to that covered by claims 105-110. Applicants have canceled claims 106-107 rendering the objection moot as to these claims.

To assist in clarifying the distinction between the inventions, Applicants respectfully direct the Examiner's attention to the declaration of Dr. Donini, submitted herewith. Exhibit B of the declaration presents infection models using peptide SEQ ID NO:7 alone or in combination with antibiotics. Specifically, pages 6-8 of Exhibit B show infection models incorporating complementary use of an antibiotic with SEQ ID NO:7.

As indicated by Dr. Donini, SEQ ID NO:7 is a complementary treatment modality to antibiotics. While antibiotics target the bacteria, SEQ ID NO:7 activates the host's innate immune system to 1) therapeutically treat an established infection; or 2) prophylactically to protect patients at high risk for developing infection. Figure 1 of the specification and Figure 12 of Exhibit B show administration of SEQ ID NO:7 in combination with an antibiotic prior to infection. The Figures indicate that administration of SEQ ID NO:7 prior to infection, works to stimulate the host immune response and lower bacterial counts where administration of antibiotics alone is insufficient to eradicate an infection.

Exhibit B of the declaration also shows that antibiotic administration is occasionally given prophylactically to patients at high risk for developing an infection (for example, patients which have undergone autologous stem cell transplantation are often given prophylactic antibiotics during their recovery period in addition to GM-CSF). Dr. Donini indicates that prophylactic administration of antibiotics, while necessary in some cases, does increase the likelihood of engendering antibiotic resistance, limiting the lifetime of current antibiotics and creating "superbugs". Thus, in these situations, it is advantageous to administer SEQ ID NO:7 and related peptides, thereby inducing a more effective immune response. Exhibit B further demonstrates that SEQ ID NO:7 is prophylactically effective in immune-compromised situations (see e.g., Figures 13a and 13b of Exhibit B, demonstrating prophylactic administration of SEQ ID NO:7).

Applicants respectfully submit that the declaration of Dr. Donini, clarifies the difference between the invention of claim 93 and that of claims 105-110. Accordingly, withdrawal of the rejection of claims 93 and 99-104 under 35 U.S.C. §112, second paragraph is respectfully requested.

Applicants respectfully traverse the rejection of claims 103 and 110 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Action alleges that it is unclear what is meant by "the peptide sequence is reversed". Applicants respectfully direct the Examiner's attention to the specification at paragraph [0067] which discusses the scope of cationic peptides envisioned. Paragraph [0067] states:

> Peptides of the invention include any analog, homolog, mutant, isomer, or derivative of the peptides disclosed in the present invention, so long as the bioactivity as described herein remains. Also included is the **reverse** sequence of a peptide encompassed by the general formulas set forth above.

The specification clearly contemplates the scope of peptides covered by the invention to include peptides having the reverse sequence of those disclosed. Accordingly, withdrawal of the rejection of claims 103 and 110 under 35 U.S.C. §112, second paragraph is respectfully requested.

Applicants respectfully traverse the rejection of claims 102 and 109 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Action alleges that it is unclear where the cyclization is to be performed of SEQ ID NO:7. Applicants respectfully submit that the term "cyclized", as recited in the claims, is a term of art and would be known to one of skill in the art as would general methods for cyclizing. Applicants direct the Examiner's attention to paragraph [0067] of the specification which states

that "the peptide may be cyclized chemically or by the addition of two or more cysteine residues with the sequence and oxidation to form disulphide bonds." Moreover, as indicated in the declaration of Dr. Donini, one of skill in the art would also know that cyclization may be performed in a "head to tail" fashion. Accordingly, Applicants submit that one of skill in the art would understand the metes and bounds of the invention, and respectfully request that the rejection be withdrawn.

Conclusion

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

The Commissioner is hereby authorized to charge $525.00 as payment for the three-month Extension of Time fee and any other fees associated with the filing submitted herewith, or credit any overpayments to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

Date: October 4, 2007

Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA PIPER US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer No. 28213